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Response to: "What is the meaning of non-linear dose–response relationships between blood lead concentrations and IQ?"

Todd A. Jusko
Department of Epidemiology University of Washington

David W. Lockhart
Department of Biostatistics University of Washington

Paul D. Sampson
Department of Statistics University of Washington

Charles R. Henderson Jr.
Department of Human Development Cornell University

Richard L. Canfield
Division of Nutritional Sciences Cornell University

Dear Dr. Cranmer:

Studies of pediatric lead exposure and IQ suggest that the association between measured blood lead concentrations and IQ is nonlinear, with the decline in IQ greater at lower levels of exposure (Bellinger and Needleman, 2003; Canfield et al., 2003; Jusko et al., 2005; Lanphear et al., 2005). In their recent paper, Bowers and Beck (2006) claim to show that this nonlinearity is artificial because a nonlinear dose-response function is an inevitable result of any regression on data with the distributional characteristics common to these studies. To support this claim, the authors conduct a demonstration by matching the nth percentile of lognormally distributed lead with the (100-n)th percentile of normally distributed IQ and show that the resultant regression line has a nonlinear slope similar in shape to those reported by Canfield et al. (2003) and Lanphear et al. (2005). From this result they conclude that "any environmental measure that is lognormally distributed and any cognitive score that is normally distributed will by necessity have a non-linear slope." This argument is fundamentally flawed owing to a misunderstanding of the meaning of a statistical regression model. Equally important is that, regardless of how one evaluates their claim about nonlinearity, the most important conclusions from studies of pediatric lead exposure are not fundamentally altered.

Bowers and Beck make use of a peculiar approach in which they match on the percentiles of marginal distributions. This procedure obscures the distinction between systematic and random components of variation that is essential to regression analysis, which by definition concerns the (conditional) expectation of the dependent variable (here IQ) in terms of values of predictor variables, including blood lead concentration. The nature of the relationship between IQ and blood lead (and other predictors) specified by some function, possibly nonlinear in the parameters, is *not* defined or estimated by matching percentiles of the distributions of the

Corresponding author: Todd A. Jusko University of Washington Box 357236 Seattle WA 98195 Tel: (206) 616-1457 Fax: (205) 543-8525 jusko@u.washington.edu.

dependent and independent variables. Hornung et al. (2006) provide an apt critique of the problem with the method of matching percentiles.

Aside from their questionable methodology, Bowers and Beck make several assumptions that have little relevance to the data they purport to address. For instance, they assume that "changes in blood lead account for all observed variability in IQ." Decades of research on the association between lead and IQ suggests that, on average, lead accounts for less than 5% of the variance in IQ (Koller et al., 2005). While they do discuss the possibility of other covariates, they do not relax the Gaussian distributional assumption for these covariates. Thus, without some statement about random error and more detailed examination of other variables in the model, Bowers and Beck's assumption of matching percentiles makes no sense or is trivially false in real data. Their caution regarding the extreme ends of the distributions does not suffice.

A linear function $f(x) = a + bx$, together with a lognormal distribution for x and normally distributed unexplained variation e, does not in general result in a normally distributed outcome y. However, Bowers and Beck assume that lead and IQ follow theoretical lognormal and normal population distributions, respectively, across studies and sampling frames and that these population distributions are relevant for regression analysis. It is not generally true that sample distributions will follow theoretical, population-based distributions. As occurs in most epidemiological studies, the Rochester study had exclusion criteria that limited enrollment to a subpopulation that has important differences from the general U.S. population. For example, the Rochester study sampled from a socio-economically disadvantaged population residing in inner-city Rochester. Exclusion criteria such as low birth weight, preterm birth, and neurodevelopmental abnormalities limited the number of children at increased risk of cognitive deficits in the sample, truncating the left tail of the IQ distribution. Thus, the assumption that IQ (and perhaps even blood lead) will follow theoretical distributions is untenable and is irrelevant to epidemiological studies that have various inclusion and exclusion criteria related to the exposures and outcomes of interest.

To examine Bowers and Beck's approach, we simulated data for a true linear regression relationship using parameters that reflect characteristics of the Rochester data. We drew 305 blood lead values from a lognormal distribution corresponding to the blood lead concentration parameters observed in the Rochester cohort at 3 and 5 years of age (Canfield et al., 2003). To obtain the corresponding IQ values, we estimated the least squares linear regression of IQ on the blood lead data (rather than the nonlinear regression reported by Canfield et al., 2003) and added an independent, normally distributed error term to each value with variance reflecting the variance of the residuals for the regression model reported by Canfield et al. (2003). Figure 1 shows a plot of the simulated IQ and lead values, the ordinary least-squares regression line, and a smoothing spline similar to the one reported in Canfield et al. (2003).

The figure illustrates the linear relation between lognormally distributed blood lead and IQ. The correspondence between the linear fit and the spline indicates that a linear function fits these data well. Contrary to the assumption by Bowers and Beck, the 90th percentile of blood lead (12.8 μg/dL), for example, corresponds not to the 10th percentile of IQ (75), but to approximately 87, or the 37^{th} percentile of IQ. These results show that the nonlinearity observed in Canfield et al. (2003) is not a "mathematical requirement" of the observed lead and IQ distributions, but a falsifiable empirical result.

While the simulation shown here provides a counterexample to the claim of Bowers and Beck, more comprehensive simulations in which distributional parameters and covariate structures are systematically varied could be used to address the question of how frequently or how rarely nonlinearity results under Bowers and Beck's scenario.

We are in full agreement with Bowers and Beck regarding the need for caution in interpreting findings without a clear biological basis. This caution is not aided, however, by a flawed argument about percentile matching for (irrelevant) theoretical marginal distribution models. While it is appropriate to review critically the increasing number of reported findings of nonlinear blood lead–IQ relationships, any challenge to the shape of the blood lead–IQ relationship should be based on details of the statistical methods and a critique of the (usually unverifiable) assumptions underlying the models (for example, additivity and linearity of confounders in the model).

Finally, Bowers and Beck suggest there is doubt whether "a dose-response relationship …in fact even exists in this region [of exposure]." We note in passing that the research is quite conclusive that very low blood lead concentrations in children—concentrations well below the current CDC level of concern—are associated with subtle deficits in neurobehavioral function that can have important effects on children's life paths (Canfield and Jusko, in press; Gilbert and Weiss, 2006), irrespective of the issue of nonlinearity; Bowers and Beck do not in any way address this.

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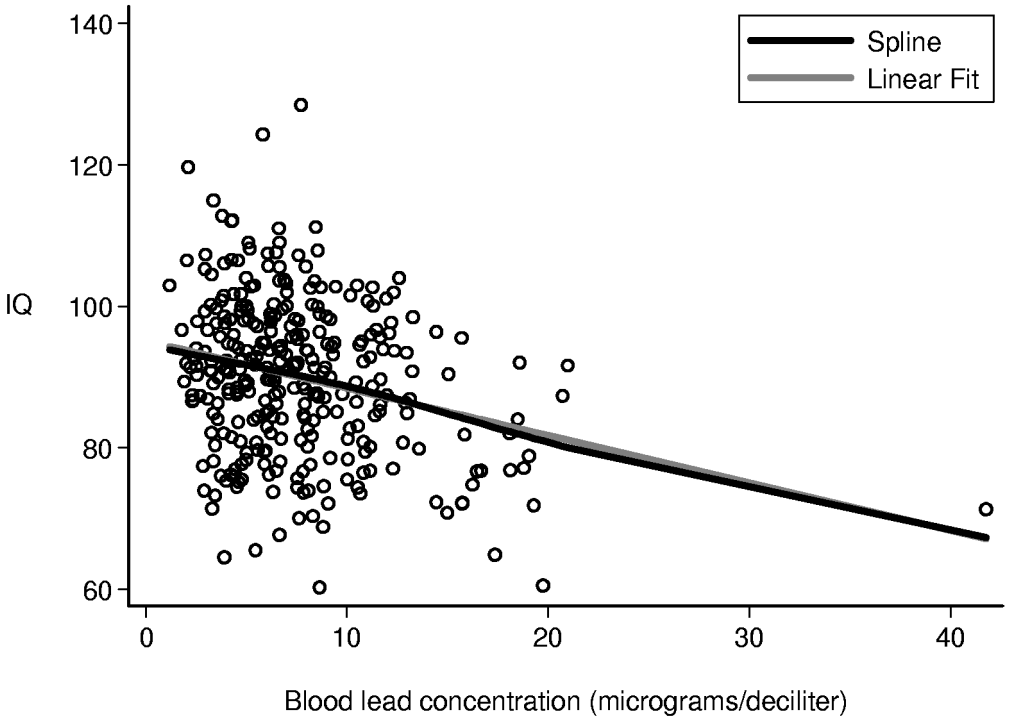

Figure 1.
Simulated blood lead concentrations and IQ from Canfield et al., (2003).